The Human Amygdala and Pain: Evidence From Neuroimaging

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Abstract: The amygdala, a small deep brain structure involved in behavioral processing through interactions with other brain regions, has garnered increased attention in recent years in relation to pain processing. As pain is a multidimensional experience that encompasses physical sensation, affect, and cognition, the amygdala is well suited to play a part in this process. Multiple neuroimaging studies of pain in humans have reported activation in the amygdala. Here, we summarize these studies by performing a coordinate-based meta-analysis within experimentally induced and clinical pain studies using an activation likelihood estimate analysis. The results are presented in relation to locations of peak activation within and outside of amygdala subregions. The majority of studies identified coordinates consistent with human amygdala cytoarchitecture indicating reproducibility in neuroanatomical labeling across labs, analysis methods, and imaging modalities. Differences were noted between healthy and clinical pain studies: in clinical pain studies, peak activation was located in the laterobasal region, suggestive of the cognitive-affective overlay present among individuals suffering from chronic pain; while the less understood superficial region of the amygdala was prominent among experimental pain studies. Taken together, these findings suggest several important directions for further research exploring the amygdala's role in pain processing. *Hum Brain Mapp* 35:527–538, 2014.

Key words: chronic pain; fMRI; PET; meta-analysis; experimental pain

Abbreviations: ALE, activation likelihood estimate; ASL, arterial spin labeling.

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INTRODUCTION

Pain is a complex sensory and emotional experience. While integrative function of brain circuits contribute to overall responses to sensory, emotional and cognitive processing, the understanding of how specific regions function in pain processing may contribute to a better understanding of brain function in pain. One such region is the amygdala (Rouwette et al., 2011; Toyoda et al., 2011). The amygdala is a complex, small deep brain structure located bilaterally in the medial temporal lobe. Due to its role in emotional processing (Costafreda et al., 2008), it has garnered considerable research attention. Fear conditioning and regulation are perhaps the most well-known emotional processes associated with the amygdala (LeDoux, 2003; Sehlmeyer et al., 2009), although its role has been extended to multiple areas of functioning including reward learning and motivation (Murray, 2007). In addition, structural and functional changes in the amygdala are associated with a variety of psychiatric disorders, including anxiety (Etkin and Wager, 2007) and depression (Sacher et al., 2011). The anatomy of the amygdala (Sah et al., 2003), and its relevance to emotional processing (Costafreda et al., 2008; Sergerie et al., 2008) and anxiety (Etkin and Wager, 2007) have been extensively reviewed.

In this article, we review the growing human neuroimaging literature that has linked the amygdala with pain. Pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage (http://www.iasp-pain.org). Thus pain is a multidimensional experience characterized by clear physiological and psychological elements (Gatchel et al., 2007). While accumulation of data on the amygdala's role in sensory processing has been defined in preclinical research (Bernard et al., 1992; Huang et al., 1993; Ren and Neugebauer, 2010), the integration of evolution of nociception into pain with its emotional context and complexity is more difficult in non-human studies. The emotional context can affect both subjective pain sensitivity and nociceptive processing. The amygdala's contribution to pain and its affective dimension is emerging (Lumley et al., 2011; Neugebauer et al., 2004, 2009).

This review aims to provide an overview of neuroimaging pain studies implicating the amygdala in acute and persistent pain responses, determine if activation in distinct subregions can be differentiated, and describe how these activations could impact our understanding of how specific subdivisions contribute to pain function and provide a basis for improved translational research. The review is divided into the following sections: (1) First, a brief overview of amygdala anatomy and connections in relation to pain is provided for neurophysiological context; (2) Second, we describe functional imaging meta-analysis methods using an activation likelihood estimate (ALE) approach; (3) Third, we discuss the results and findings applying ALE analysis and discuss our observations regarding the success of this methodology in our current investigation.

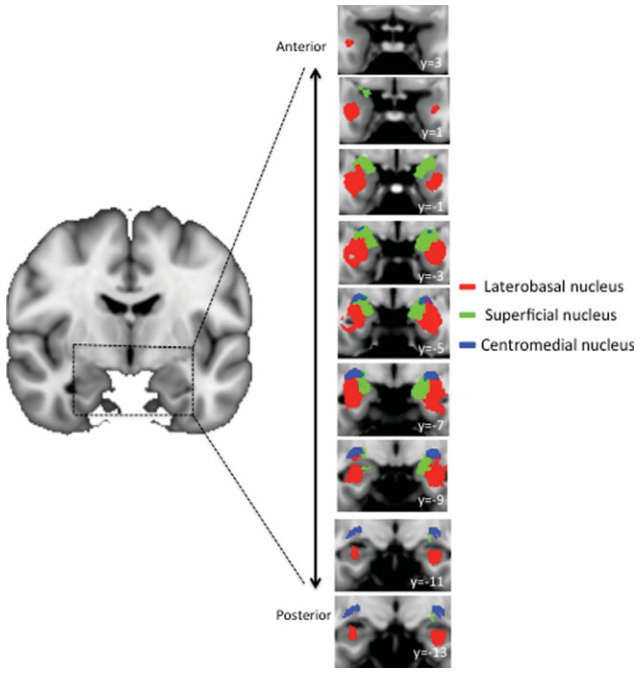

Figure 1.

Serial coronal views of amygdala cytoarchitecture. The whole-brain coronal slice at $y = -7$ is pictured above. Each subregion of the amygdala was masked using the Julich Histological Atlas (JHA) (Eickhoff et al., 2005) with at 50% or greater likelihood cutoff. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Amygdala Anatomy

The amygdaloid complex has been extensively studied in non-humans (Sah et al., 2003), with recent advances in imaging techniques facilitating the closer examination of the amygdala *in vivo* in humans. The amygdala consists of a set of nuclei, and the segmentation of its components has been widely studied (Alheid, 2003; Alheid et al., 1998; Amunts et al., 2005). Cytoarchitectonic studies support segmenting the amygdala nuclei into three main groups: (1) superficial (volume = 334 ± 81 mm^3 right, 319 ± 61 mm^3 left), (2) laterobasal (volume = 1063 ± 214 mm^3 right, 1050 ± 219 mm^3 left), and (3) centromedial (volume = 138 ± 31 mm^3 right, 138 ± 28 mm^3 left) (Amunts et al., 2005) (see Fig. 1) (Schumann et al., 2011). Very recently, this parcellation was corroborated in humans using both diffusion tensor imaging and high resolution structural imaging (Solano-Castiella et al., 2010, 2011). The superficial subdivision lies adjacent to the laterobasal group and includes cortical nuclei involved with olfaction (Sah et al., 2003). The laterobasal complex consists of the lateral, laterobasal, basomedial, and basoventral nuclei. These nuclei are most involved with associative learning processes, such as fear

conditioning through afferents from cortical and subcortical regions that include the hippocampus, thalamus, and prefrontal cortex (LeDoux, 2003). The centromedial nuclei play a significant role in generating behavioral responses through projections to the brainstem, as well as cortical and striatal regions, like the caudate (LeDoux, 2007). Although the "extended amygdala" is at times referred to as a region within the amygdala complex, it is also described as the bed nucleus of the stria terminalis that receives afferent projections from the centromedial region (Alheid, 2003). Debates continue regarding what should be considered part of the amygdala complex (Swanson and Petrovich, 1998), and the current review will focus on the basolateral, superficial, and centromedial regions.

Amygdala Connectivity

The afferent and efferent connections of the amygdala are extensive. Each amygdala nucleus receives inputs from multiple brain regions (McDonald, 1998) and efferent projections from the amygdala are widespread, including cortical and subcortical regions (Pitkanen et al., 2000). The lateral nucleus of the laterobasal complex is often viewed as the gatekeeper of the amygdala, receiving excitatory inputs from visual, auditory, somatosensory (including pain), olfactory, and taste systems in the sensory thalamus and cortex. Although the lateral nucleus receives the majority of afferent connections in the amygdala, other areas of the laterobasal complex receive input with primary projections from the prefrontal and medial frontal cortices (Stefanacci and Amaral, 2002). The centromedial nuclei play a prominent role in efferent connections, but tracing studies also identify this region as a major receiver of purely nociceptive signals (Gauriau and Bernard, 2004). The superficial subdivision of the amygdaloid complex primarily receives olfactory input (Sah et al., 2003).

As for efferent connections, the central nucleus predominantly projects to the hypothalamus, bed nucleus of the stria teminalis, midbrain periaqueductal gray, pons, medulla, and brain stem. These structures are involved with the expression of innate emotional and associated physiological sequelae as observed in fear conditioning encompassing behavioral (e.g., freezing), autonomic (e.g., heart rate) and endocrine (pituitary-adrenal hormones) responses. A high degree of intra-amygdala communication occurs where sensory information received through the lateral amygdala typically travels through the basal nucleus to ultimately reach the central nucleus. Additional pathways feed in from the lateral and basal nuclei through the intercalated cells, to inhibit neurons in the central nucleus. An additional set of output connections stem from the basal nucleus to the medial temporal lobe memory system, the striatal areas involved in the control of instrumental behaviors, and the prefrontal cortex. Cortical nuclei of the superficial region reciprocally project back to the olfactory cortex and recent functional connectivity findings demonstrate patterns of activity synchronized with the limbic region, which suggest that olfactory processes associated with the cortical nuclei of the superficial group may play an affective role in humans, as has been observed in animals (Roy et al., 2009).

Pain-Related Amygdala Circuitry

With the amygdala playing a pivotal role in negative affect, it is not surprising that emerging research implicates amygdala circuitry in pain processing. The lateral and laterobasal nuclei of the laterobasal complex and the central nuclei have been identified as particularly important for nociceptive signal transmission (see Fig. 2). Nociceptive information reaches the lateral capsular division of the central nucleus through the spino-parabrachio-amygdaloid pain pathway either directly from lamina I of the spinal and trigeminal dorsal horns, or more commonly through the parabrachial complex (Bernard et al., 1993; Gauriau and Bernard, 2004). Polymodal sensory, including nociceptive, inputs from the thalamus and cortex (e.g., insula, anterior cingulate) target the lateral nuclei (Phelps and LeDoux, 2005; Shi and Cassell, 1998). Associative processing in the lateral-basolateral network is believed to attach emotional significance to sensory information, thus playing an important role in fear and anxiety (Pare et al., 2004). This information is then transmitted to the central nucleus, which modulates pain behavior through signals sent to descending pain control centers in the brain (Neugebauer et al., 2009). In addition, the amygdala is also closely connected to cortical areas, with the laterobasal region projecting to prefrontal cortical areas (Price, 2003), thus suggesting that the amygdala contributes not only to the emotional-affective, but also the cognitive aspects of pain including memories and expectations for pain. The cingulate gyrus, which is also related to affective processing, selection of motor responses, and memory to predict and avoid pain (Devinsky et al., 1995; Vogt, 2005), has dense connections with the amygdala (Devinsky et al., 1995; Kobayashi, 2011). In addition, projections from the contralateral insula to the central nucleus of the amygdala have been reported (Jasmin et al., 2003). Thus, the amygdala receives afferent nociceptive information from the spinal cord and trigeminal system, as well as information from subcortical areas and cortical areas. It is well positioned to modulate some of the properties of pain (cognition, fear, anxiety etc.) that relate to aversion and negative affective behaviors related to pain. Clearly the data on amygdala interactions with other parts of the neural axis are complex but clearly indicate a pivotal role for the structure in evaluation and emotional processing of pain. The ability to integrate data from humans (e.g., connectivity) and evaluate specific circuits in animals will improve our basic understanding of this complexity.

Neuroimaging research of pain processing is growing tremendously, with the primary and secondary somatosensory cortex (S1 and S2), spinal cord, thalamus, insula, anterior cingulate cortex, and prefrontal cortex consistently identified (Apkarian et al., 2005; Peyron et al., 2000;

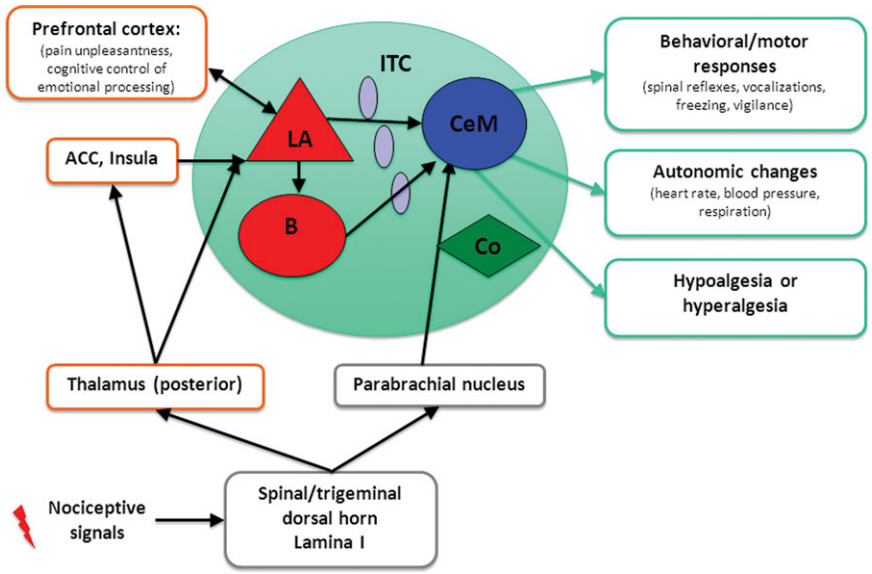

Figure 2.

Nociceptive pathways involving the amygdala. Orange signifies areas significantly affected in chronic pain. ACC = anterior cingulate cortex, B = basal nucleus, CeM = centromedial nuclei region, Co = cortical nuclei in the superficial region, ITC = intercalcated cells, LA = lateral nucleus. Based on (Neugebauer et al., 2009; Neugebauer et al., 2004; Price, 2003). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Tracey, 2008). Emerging imaging research also implicates midbrain areas (e.g., periaqueductal gray) (Linnman et al., 2011), the cerebellum (Moulton et al., 2010), and subcortical structures including the hippocampus, basal ganglia, and amygdala (Borsook et al., 2010; Schweinhardt and Bushnell, 2010). While a number of studies show amygdala activation, few have focused on the area in human imaging as it relates to pain and analgesia (Upadhyay et al., 2010). Advances in neuroimaging techniques in humans have allowed for not only a better understanding of the functional connectivity of the amygdala but also improved visualization of its cytoarchitecture. To evaluate data from the literature on activation in the human amygdala we have: (1) compiled human functional neuroimaging findings that identified amygdala activation in pain processing; (2) submitted these findings to a coordinate-based meta-analysis using GingerALE; and (3) explored potential activation patterns among amygdala subregions based on pain in healthy patients and those with clinical pain.

METHODS

Search Criteria

Articles were identified by searching Pubmed (http:www.ncbi.nlm.nih.gov/pubmed/), limiting the search to functional imaging in humans, and using the following terms: "Amygdala and Pain and fMRI" (n = 151); "Amygdala and Pain and Positron Emission Tomography" (n = 40). In addition, we searched pain imaging review articles and carefully examined the references of all retrieved articles for other potentially relevant studies. Only categorical contrasts were included. Studies on healthy participants and clinical pain patients were included. Activation findings from pharmacological challenges or associated with experimental manipulations (e.g., olfaction, visual stimuli) were excluded.

Analysis

From each manuscript, we extracted sample size, study population, gender distribution, methods, and coordinates of regions reported as amygdala. Coordinates reported in Talairach space (n = 14) were converted to MNI space using the Lancaster icbm2tal algorithm (Laird et al., 2010; Lancaster et al., 2007). Activation likelihood estimates were calculated using GingerALE 2.1.1 (Eickhoff et al., 2009). This algorithm identifies areas showing a convergence of activation foci across different experiments that are higher than expected under the null distribution of a random spatial association (Turkeltaub et al., 2002). We apply the ALE analysis in a novel manner by focusing on a small, single brain region and will discuss our observations regarding the success of this methodology in the current investigation.

Imaging Acquisition and Analysis

For fMRI imaging, one study was performed in a 1T scanner, 14 studies were performed in a 1.5T scanner, and

TABLE I. Functional neuroimaging of amygdala activation in experimental pain studies

Paper	Method	Subjects	Stimulation	Site	Foci	Smoothing	Signal
Baliki et al., 2009	3T fMRI	14 (7F)	Thermode	Back	2(B)	5mm	In
Becerra et al., 1999	1.5T fMRI	12M	Thermode	L hand	2 (B)[a]	NR	D
Berman et al., 2008	1.5T fMRI	12F	Rectal distention	Rectum	1 (right)	5mm	D
Bingel et al., 2002	1.5T fMRI	14(1F)	Laser	R/L hand alternating	2 (B)	6mm	In
Bingel et al., 2006	1.5T fMRI	19 (4F)	Laser	R/L hand alternating	2 (B)	8mm	In
Bornhovd et al., 2002	1.5T fMRI	9(3F)	Laser	L hand	2 (B)	6mm	In
Carlsson et al., 2006	1.5T fMRI	9(5F)	Electric shock	R wrist	1 (C)	12mm	In
Derbyshire et al., 1997	PET	12(6F)	Laser	R hand	2 (B)	10mm	D
Dimitrova et al., 2003	1.5T fMRI	16(5f)	Electric	L tibial nerve	NR	6mm	In
Dube et al., 2009	1.5T fMRI	9(3F)	Thermode	L leg	1 (I)	8mm	In
Iadarola et al., 1998	PET	13(5F)	mechanical allodynia post capsaicin injection	L volar forearm	1 (I)	NR	In
Kulkarni et al., 2005	PET	17M	Laser	L dorsal forearm	1 (C)	16mm	In
Kupers et al., 2004	PET	10 (4F)	5% solution of hypertonic saline	R masseter muscle	1 (I)	12mm	D
Lu et al., 2004	3T fMRI	10(2F)	Gastric pain via balloon	Abdomen	1 (right)	8mm	In
Mainero et al., 2007	3T fMRI	12M	mechanical allodynia post capsaicin injection	R Trigeminal nerve	2 (B)	4mm	In
Mobascher et al., 2009	3T fMRI	20M	Laser	L hand	1(C)	6mm	In
Mohr et al., 2005	1.5T fMRI	16M	Thermode	R hand	1 (I)	8mm	In
Petrovic et al., 2004	PET	10M	Cold pressor (1-glycol; 1-ice)	L hand	2 (B)	10mm	D
Peyron et al., 2007	1T fMRI	9M	Electric	L leg	1 (C)	10mm	In
Schneider et al., 2001	1.5T fMRI	6M	Vascular pain via balloon	Dorsal vein L foot	1 (C)	6mm	In
Seminowicz and Davis, 2006	1.5T fMRI	22 (12F)	TENS	Left median nerve	1 (C)	6mm	In
Takahashi et al., 2011	3T fMRI	13M	Electrical stimulation	L Tibial muscle	2 (B)	8mm	In
Yoshino et al., 2010	1.5T fMRI	15(6F)	Electric intraepidermal	L forearm	1 (C)	8mm	In

[a]Did not report foci coordinates.B = bilateral, C = contralateral to stimuli, D =decreased signal, I = ipsilateral to stimuli, In=increased signal; NR = not reported.

eight in 3T scanners; accordingly the resolution of the images varied from 7 mm to 1 mm. Spatial smoothing across fMRI studies ranged from a Gaussian kernel of 5 mm to 12 mm full width half-maximum. Eleven investigations were PET cerebral blow flow studies. Spatial smoothing across PET studies ranged from a Gaussian kernel of 10 mm to 20 mm full width half-maximum. One investigation used arterial spin labeling (ASL) with a 3T scanner to measure cerebral blood flow. Specific details regarding scanner type and smoothing for each study is detailed in Tables I and II.

RESULTS

Included Experimental Studies

After review of the retrieved articles and cross-references, we identified 23 experimental pain studies that fit our criteria (21 with activation coordinates reported). We further divided the studies for ALE analysis based on increased or decreased signal detected. Among experimental studies with coordinates reported, 17 reported an increased signal and 4 reported a decreased signal; these studies and studies without activation coordinates are detailed in Table I.

Increased signal

There were 227 participants across 17 studies included in the ALE analysis. Among them, 79% were male and 21% were female. Experimental pain was induced in all studies with healthy participants. Pain induction method included: laser ($n = 5$), electrical ($n = 5$), thermode ($n = 3$), distension ($n = 2$; vascular, gastric), and mechanical allodynia ($n = 2$). Increased amygdala signal was observed bilaterally in six studies (2 = bilateral stimuli, 2 = left side stimuli, 1 = right, 1 = midline [back]). Right hemispheric increases were observed in eight studies (6 contralateral to stimuli, 1 = ipsilateral, 1 = midline [abdominal distension]). The left hemisphere increases were detected in three studies (2 = contralateral to stimuli, 1 = ipsilateral).

TABLE II. Functional neuroimaging of amygdala activation in clinical pain studies

Paper	Method	Subjects	Stimulation	Condition	Foci	Smoothing	Signal
Baliki et al., 2008	3T fMRI	5 (1F)	Pressure on affected knee	Osteoarthitis	1 (left side)	5mm	In
Berman et al., 2008	1.5T fMRI	14F	Rectal distention	IBS	2 (B)	5mm	D
Bonaz et al., 2002	1.5T fMRI	11 (10F)	Rectal distension	IBS	1 (right side)	NR	D
Derbyshire et al., 1999	PET	6M	Thermode on R hand	Post-Surgical Dental Extraction	1 (I)	20mm	D
Geha et al., 2007	3T fMRI	11(10F)	Spontaneous	Post-herpetic neuralgia	2 (B)	5mm	In
Geha et al., 2008	3T fMRI	11(9F)	Dynamic mechanical allodynia on affected side	Post Herpetic Neuralgia	1 (I)	5mm	In
Giesecke et al., 2005	1.5T fMRI	7F	Pressure pain L thumb	Fibromyalgia +MDD	2(B)	6mm	In
Gundel et al., 2008	1.5T fMRI	12F	Thermode on L forearm	Somatoform pain disorder	1(C)	8mm	In
Howard et al., 2011	3T fMRI/ ASL	16M	spontaneous	Third molar extraction	2 (B)	NR	In
Kulkarni et al., 2007	PET	12(6F)	spontaneous	Osteoarthritis	1 (left side)	16mm	In
Kulkarni et al., 2007	PET	12(6F)	Thermode above affected knee	Osteoarthritis	2 (B)	16mm	In
Naliboff et al., 2003	PET	42(23F)	Rectal distention	IBS	1 (left side)	12mm	F In; M D
Mayer et al., 2005	PET	7M	Rectal distention	IBS	1 (left side)	12mm	In
Petrovic et al., 1999	PET	5(3F)	Dynamic mechanical allodynia on affected limb	Mononeuropathy	2 (C), 1 (I)	16mm	D
Wilder-Smith et al., 2004	1.5T fMRI	5F	Rectal distention	IBS -Constipation	2(B)[a]	NR	D
Wilder-Smith et al., 2004	1.5T fMRI	5F	Rectal distention + Ice water foot bath (DNIC)	IBS-Constipation	2(B)[a]	NR	In

[a]Did not report foci coordinatesB = bilateral, C = contralateral to stimuli, D = decreased signal, DNIC = diffuse noxious inhibitory control, IBS = irritable bowel syndrome, I = ipsilateral to stimuli, In = increased signal, MDD = Major Depressive Disorder; NR = not reported.

Decreased signal

There were 44 participants across four studies. Due to the small number of studies and participants, we did not conduct an ALE analysis. There were equal numbers of males ($n = 22$) and females ($n = 22$). Pain induction methods differed across all four studies to include cold pressor, hypertonic saline, laser, and rectal distension. Decreased amygdala signal was observed bilaterally in two studies (1 = right side stimuli, 1 = left). Right hemisphere decreases were observed in two studies (1 = ipsilateral to stimuli, 1 = midline [rectum]).

Included Clinical Pain Studies

We identified 17 studies (15 with activation coordinates reported) clinical pain studies, 10 reported an increased signal and five reported a decreased signal; these studies and studies without activation coordinates are detailed in Table II.

Increased signal

There were 116 participants across 10 studies included in the ALE analysis. Among them, 36% were male and 64% were female. Pain conditions included: osteoarthritis ($n = 3$), irritable bowel syndrome ($n = 2$), postherpic neuralgia ($n = 2$), and one each of the following: dental pain, somatoform pain, and fibromyalgia with comorbid depression. Pain induction methods included: thermode ($n = 2$), rectal distension ($n = 2$), pressure ($n = 2$), and mechanical allodynia ($n = 1$). In three studies no pain induction method was used. Increased amygdala signal was observed bilaterally in four studies (2 = stimuli applied to affected side, 1 = left, 1 = no stimuli). The left hemisphere increases were observed in five studies (1 = stimuli

TABLE III. Activation likelihood estimates for coordinates reported as the amygdala across all increased signal studies and divided between experimental pain and clinical pain studies

					MNI Coordinates			
Function	Subjects	Experiments	Foci	Cluster	x	y	z	Anatomic label
Experimental pain	227	17	23	1	20	−2	−18	78% Amy_superficial group R, 20% Amy_ laterobasal group R, 9% Amy_centromedial group R
				2	−24	0	−16	46% Amy_superficial group L; 9% Amy_centromedial group L
Clinical Pain	116	10	14	1	−22	−6	−16	89% Amy_laterobasal group L, 43% Amy_superficial group L, 16% Amy_centromedial group L, 10% Hippocampus subiculum L
				2	22	0	−16	68% Amy_superficial group R, 15% Amy_laterobasal group R, 10% Hippocampus entorhinal cortex R

Amy = amygdala.

applied affected side, 2 = midline [rectum], 2 = no stimuli). In one study, increased signal in the right amygdala was detected contralateral to stimuli.

Decreased signal

There were 59 participants across five studies. Due to the small number of studies and participants, we did not conduct an ALE analysis. Descriptively, there were almost equivalent numbers of males (n = 32) and females (n = 27). Pain conditions included: irritable bowel syndrome (n = 3), dental pain (n = 1), and mononeuropathy (n = 1). Pain induction methods included rectal distension (n = 3), mechanical allodynia (n = 1), and thermode (n = 1). Decreased amygdala signal was observed bilaterally in one rectal stimuli study. Left hemisphere decreases were observed in another rectal stimuli study. In two studies right hemisphere decreases were noted (1 = ipsilateral to stimuli, 1 = midline [rectum]). Finally, one study with a series of experiments observed right and left hemisphere decreases separately with stimuli applied to the affected side.

Amygdala Coordinate Distribution—Experimental Pain

Increased signal

Two clusters with one focus each were detected from the meta-analysis (Table III and Fig. 3). The first cluster was primarily seated in the superficial region of the right amygdala (78%) and the second cluster was seated in the superficial region of the left amygdala (46%). Additional probabilities were noted in the laterobasal and centromedial regions of the right and left amygdala for both clusters. No other brain areas were noted.

Decreased signal

Due to the small number of decreased signal studies, we did not conduct an ALE analysis. Activation coordinates across these studies in comparison to increased signal studies are plotted in Figure 5.

Amygdala Coordinate Distribution—Clinical Pain

Increased signal

Two clusters with one focus each were detected from the meta-analysis (Table III and Fig. 4). The first cluster was primarily seated in the laterobasal region of the left amygdala (89%) with additional probabilities noted in the

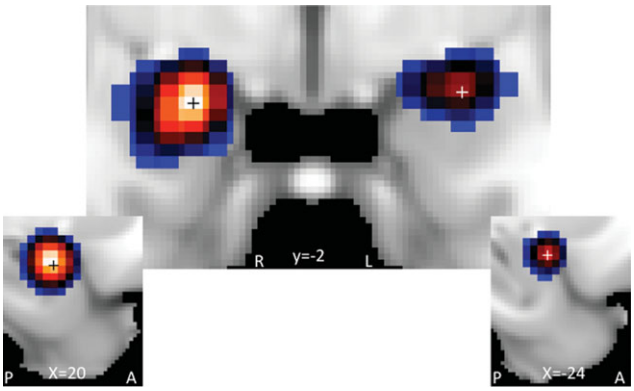

Figure 3.
Amygdala activation in healthy subjects. Increased signal experimental pain with healthy participants from GingerALE analysis. Top images are coronal views, bottom images are sagittal. A = anterior, L = left, P = posterior, R = right. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

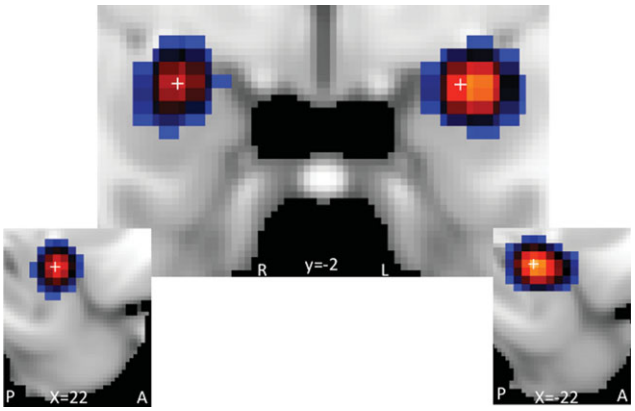

Figure 4.
Amygdala activation in clinical pain subjects. Increased signal clinical pain activation from GingerALE analysis. Top images are coronal views, bottom images are sagittal. A = anterior, L = left, P = posterior, R = right. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

superficial and centromedial regions of the left amygdala and the subiculum of the hippocampal formation. The second cluster was seated in the superficial region of the right amygdala (68%) with additional probabilities noted in the laterobasal region of the right amygdala and the entorhinal cortex of the hippocampal formation.

Decreased signal

Due to the small number of decreased signal studies, we did not conduct an ALE analysis. Activation coordinates across these studies are plotted in Figure 5.

DISCUSSION

The current investigation represents a coordinate-based meta-analysis of human functional imaging findings of amygdala activation in pain processing. Most studies in this review identified coordinates consistent with human amygdala cytoarchitecture indicating consistency in neuroanatomical labeling across labs, analysis methods, and imaging modalities.

For the ALE meta-analysis we examined increased signal activation patterns relating to experimental pain in healthy subjects and for clinical pain in patients. All findings are presented in the context of our understanding of the probabilistic cytoarchitecture of the amygdala [Juliech

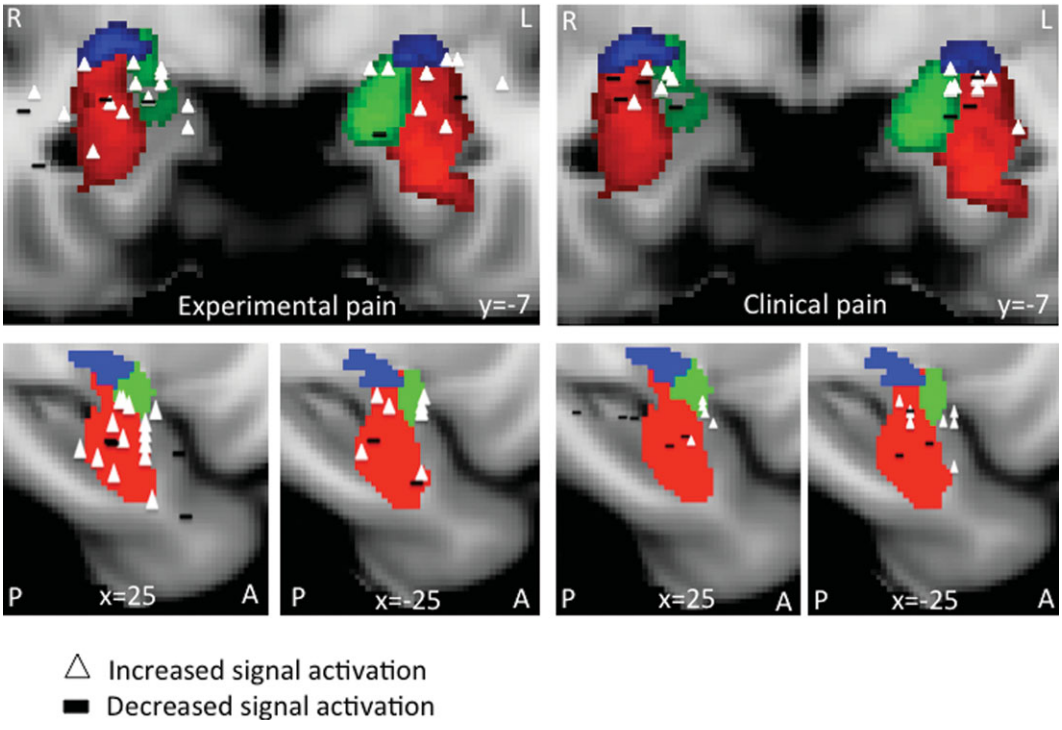

Figure 5.
Coordinate peaks reported across studies. Left images are increased and decreased signal experimental pain. Right images are increased and decreased signal clinical pain. The laterobasal (red), centromedial (blue), and superficial (green) regions are highlighted. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Histological Atlas; (Eickhoff et al., 2005) originally derived from Amunts et al. (2005)]. Increased signal experimental pain studies prominently featured bilateral superficial regions of the amygdala. Although most studies have generally limited this region's role to olfaction, recent resting state connectivity results (Roy et al., 2009) link the superficial region to other regions in the limbic lobe potentially suggesting an expanded role for this brain region. Additional considerations include that the vasculature in this area may yield greater activation independent of function, and that its relatively larger volume (334 $\pm$ 81 mm^3 right, 319 $\pm$ 61 mm^3) compared to the centromedial region (138 $\pm$ 31 mm^3 right, 138 $\pm$ 28 mm^3) may overshadow the latter regions' role.

In contrast, increased signal clinical pain studies prominently featured the laterobasal region. As white matter tracts connect the prefrontal cortex with the laterobasal region of the amygdala in tracing studies in non-human primates (Stefanacci and Amaral, 2002) and chronic pain has been linked to prefrontal lobe abnormalities (Apkarian et al., 2004), these meta-analysis findings provide further support for the role that cognition and emotion play in the context of chronic pain and is consistent with previous findings that have contrasted experimental and clinical pain studies and found enhanced affective/cognitive processing in clinical pain studies (Apkarian et al., 2005).

Although the amygdala is a brain region where increased and decreased signal in relation to pain processing is noted (Neugebauer et al., 2004), the limited number of decreased signal studies within experimental and clinical pain studies precluded conducting meta-analyses on these coordinates. Regardless, we attempt to describe these qualitative findings and plot these coordinates to facilitate hypothesis generation in future studies. Across decreased signal studies, no discernible pattern emerged for stimuli used, hemisphere activated, or gender distribution.

In exploring potentially salient patterns among increased signal in experimental and clinical pain findings, no consistently different stimulus was used between the two groups. Hemispheric activation was fairly equivalent across experimental (35%) and clinical pain (40%) for bilateral activation, with a greater proportion of right hemispheric activation among experimental studies (47% vs. 10% of clinical) compared to greater left hemispheric activation among clinical pain studies (50% vs. 17% of experimental). Although stimuli applied to the left side of the body can be attributed to the majority of experimental studies with right amygdala activation, this pattern did not emerge for clinical pain studies, where none of the left hemisphere activation was prompted by contralateral stimuli. The preponderance of right hemisphere activation among experimental pain studies is consistent with animal work that has supported the dominant role of the right amygdala in experimental pain processing within the centromedial region of the amygdala (Carrasquillo and Gereau, 2008; Ji and Neugebauer, 2009) However, several studies do not find evidence of functional lateralization in the amygdala (Robinson et al., 2010; Tran and Greenwood-Van Meerveld, 2012). With regards to gender ratios across increased signal findings there was a preponderance of males (79%) in experimental pain studies and females (64%) in clinical pain studies. It is not clear whether this disparity was a result of recruitment approach or may be suggestive of differential activation patterns among males and females. More research is needed with equal male/female gender ratios in study samples to explore potential underlying differences.

The centromedial region was identified with a small probability across three of four foci, likely due to its small size and potentially transient response, despite its essential role in amygdala function. As the centromedial region is a key area for threat detection, it is possible that the amygdala responds quickly (Cheng et al., 2007) and transiently as a threat detector that may habituate over prolonged pain stimuli or repeated pain exposures (Alvarez et al., 2011). Despite its lesser prominence across all findings, it was identified across both foci in experimental pain studies in the ALE analysis, which is consistent with its role in pure nociception (Gauriau and Bernard, 2004). The centromedial region is also more closely linked to autonomic responses, which are observed to a greater extent in acute pain situations as compared to persistent pain where sympathetic responses have been found to be blunted (Swanson and Petrovich, 1998).

Limitations

There are some important caveats to this meta-analysis: to provide sufficient statistical power, it is suggested that ALE meta-analyses have about 10–15 experiments (Laird et al., 2009). Our analysis met this criterion, but was applied to one small brain region rather than a whole-brain analysis. Although the peak activations were inherently close together, multiple clusters were derived for both experimental and clinical pain studies that spanned amygdala subregions providing meta-analytic findings that can contribute to the development of new research questions. In addition, all derived clusters were consistent with amygdala cytoarchitecture.

Regarding the nature of the BOLD response, increased and decreased signal activity may represent excitatory or inhibitory signal transmission (Logothetis, 2008) and thus additional analyses at the synaptic and cellular levels are necessary to fully understand these responses.

With regards to gender, there was a skew for a greater proportion of males in increased signal experimental studies (79%) and a greater proportion of females in increased signal clinical studies (63%), thus findings within each group may better represent amygdala function in response to pain among healthy male participants and among females with clinical pain. Although chronic pain is more common among females (34%) as compared to males (27%) (Johannes et al., 2010), the discrepancy in this meta-

analysis may simply be due to convenience samples rather than a true reflection of gender discrepancies. Regardless, gender differences in relation to pain and amygdala function are current being pursued in animal and human studies and point to exploring this potential difference further. A recent study that examined sex hormones localized to the amygdala in rats, found that female sex hormones heightened the response to colorectal distension, suggesting that females may be more prone to at least visceral hypersensitivity (Myers et al., 2011). Another recent study indicates that pain induces periaqueductal gray to amygdala functional connectivity in men greater than in women (Linnman et al., 2011).

In addition, clinical pain studies spanned a variety of persistent pain conditions, therefore making it impossible to garner conclusions about specific clinical pain syndromes and amygdala activation patterns. Although there were multiple studies among patients with irritable bowel syndrome where amygdala activation was observed, a review of activation patterns within this patient population is necessary to discern whether the amygdala is truly an important brain region for understanding the pain experience for these patients.

Finally, we made a concerted effort to include as many articles as could be located that report amygdala activation in relation to pain, but recognize that some reports may have been missed and that other brain regions have a much larger evidence base in relation to pain processing (e.g., insula, anterior cingulate cortex). The relatively small literature that points to amygdala processing in pain (Pubmed search of "fmri AND pain AND amygdala" = 151) compared to larger bodies of literature for the insula ($n = 962$) and anterior cingulate cortex ($n = 386$) may also reflect the difficulty of imaging a small subcortical brain structure such as the amygdala. As we continue to advance imaging and analysis techniques, it is possible that the amygdala may emerge as a more prominent brain structure in relation to pain processing. These meta-analytic data encourage enhanced scrutiny of this brain structure and its subregions in relation to pain processing.

Future Directions

There are several important directions for future research. Several of the studies included in this review are a decade or more old. With the availability of improved high resolution imaging techniques, we may be able to elucidate the unique roles of amygdala subregions, such as the small cluster of centromedial neurons. Relatedly, it is possible that previous studies missed activation occurring in the amygdala that may now be identified. Further exploration of increased and decreased signal responses is necessary with studies that incorporate electrophysiological data at the synaptic level to better understand the role of the amygdala in pain processing. Given the preeminence of the structure in a number of basic functions (viz., fear, emotion, and analgesia) imaging methodologies may confer further information on the neurobiology of the amygdala in health and disease. As such this understanding may allow for targeted therapies that may modulate amygdala function to be evaluated using objective imaging readouts.

CONCLUSIONS

Altogether, the results of this meta-analysis support the role of the amygdala in pain processing. The three parcellated subregions of the amygdala, the laterobasal, centromedial, and superficial aspects were all identified among the clusters. The laterobasal region and its close connection to the prefrontal cortex were more prominently featured among clinical pain studies, perhaps reflecting the affective and cognitive aspects of persistent pain. Among experimental pain foci, the centromedial region was consistently identified, although to a lesser degree than the superficial region of the amygdala. These findings support parcellation of the amygdala in relation to function and its role in pain processing.

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